7 carbon atoms optionally substituted,
the drugs of formula A = R-T_1 - with the free valence saturated as above described, used in the compound of formula (I), has not to belong to the following classes: drugs for use in incontinence, antithrombotic drugs (ACE inhibitors), prostaglandins, antiinflammatory drugs (NSAIDS and corticosteroids) but not excluding from the antiinflammatory NSAIDS paracetamol and sulindac.

In the formula -T_B-X_2-O- of the precursor compound of B which meets test 4A and does not meet test 5, compounds wherein X_2 is equal to the R_{1B}-X-R_{2B} radical wherein R_{1B} and R_{2B}, equal to or different from each other, are linear or branched C_1-C_6 alkylenes, can be used, or X_2 is a radical wherein two alkylene chains C_1-C_4, preferably C_1-C_2, are linked to non adjacent positions of a central ring having 4 or 6 atoms, preferably 5 or 6 atoms, said ring being an unsaturated cycloaliphatic ring, or a saturated or aromatic eterocyclic ring, containing one or two heteroatoms, equal or different, selected from O, S,N. By unsaturated cycloaliphatic ring it is meant a ring that has not an aromatic character according to the Hückel's rule.
Other examples of precursor compounds of B are: 1,4-butandiol: HO-$(CH_2)_4$-OH, 6-hydroxyhexanoic acid: HO-$(CH_2)_5$-COOH, 4-hydroxybutyric acid: HO-$(CH_2)_3$-COOH, N-methyldiethanolamine: HO-$(CH_2)_2$-N(CH_3)-$(CH_2)_2$-OH, diethylenglycol: HO-$(CH_2)_2$-O-$(CH_2)_2$-OH, thiodiethylenglycol: HO-$(CH_2)_2$-S-$(CH_2)_2$-OH; 1,4 dioxane-2,6-dimethanol, tetrahydropyrane-2,6-dimethanol, 4H pyrane-2,6-dimethanol, tetrahydrothiopyrane-2,6-dimethanol, 1,4-dithiane-2,6-dimethanol, cyclohexene-1,5-dimethanol, thiazole-2,5-dimethanol, thiophene-2,5-dimethanol, oxazole-2,5-dimethanol, preferably N-methyldiethanolamine, diethylenglycol, thiodiethylenglycol.

The precursor compounds of the drug and of B are prepared according to the known methods in the prior art and described, for example, in "The Merck Index, 12a Ed. (1996), herein incorporated by reference.

The tests conducted to identify the drug corresponding to the R radical of the formula (I) are in detail the following:

Test 1 (NEM): evaluation of the gastrointestinal damage from oxidative stress induced by free radicals formed following

administration of N-ethylmaleimide (NEM) (H.G. Utley, F. Bernheim, P. Hochstein "Effects of sulphydril reagents on peroxidation in microsomes" Archiv. Biochem. Biophys. 118, 29-32 1967).

The animals (rats) are distributed in the following groups (no. 10 animals for group):

A) Control groups:

1° group: treatment: only carrier (aqueous suspension 1% w/v of carboxymethylcellulose, dose: 5 ml/Kg when the drug is administered by os, or a physiologic solution when parenterally administered, i.e. by subcutaneous, intraperitoneal, intravenous or intermuscular route),

2° group: treatment: carrier as above defined + NEM,

B) Groups treated with the drug:

group I: treatment: carrier + drug,

gruppo II: treatment: carrier + drug + NEM.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperitoneal, intravenous or intramuscular route.

The NEM dose is of 25 mg/kg in physiologic solution (sub cutaneous route) and the drug is administered one hour later, in suspension in the carrier, as a single dose which corresponds to the maximum one, or the highest still tolerated by the animals of the group of rats not pretreated with NEM, i.e. the highest administrable dose to said group at which there is no manifest toxicity in the animals, defined as a toxicity that is clearly recognizable for its symtoms. The animals are sacrificed after 24 hours and then one proceeds to the evaluation of the damage to the gastrointestinal mucosa.

The drug meets test 1, i.e. it can be used to prepare the compounds of general formula (I), when the group of rats treated with NEM + carrier + drug shows gastrointestinal damages, or in said group the gastrointestinal damages noticed are greater than those shown by the group treated with the carrier alone, or the group treated with carrier + drug, or the group treated with carrier + NEM, even though the drug pharmacotherapeutic efficacy, assayed by using specific tests, is not significantly reduced.

Test 2 (CIP): Protection parameter of endothelial cell

against the oxidative stress induced by cumene hydroperoxide (CIP).

Human endothelial cells of the umbilical vein are prepared according to an usual standard procedure. Fresh umbilical veins are filled with a 0.1% by weight collagenase solution and incubated at 37°C for 5 minutes.

Afterwards the veins are perfused with medium M 199 (GIBCO, Grand Island, NY) pH 7.4 further added of other substances, as described in the examples. The cells are collected from the perfusate by centrifugation and harvested in culture flasks T-75, pretreated with human fibronectin. The cells are then harvested in the same medium, further added with 10 ng/ml of bovine hypothalamic growth factor. When the cells of the primary cell culture (i.e. that directly obtained from ex-vivo) form a single layer of confluent cells (about 8,000,000 cells/flask), the culture is stopped and the layers washed and trypsinized. The cellular suspensions are transferred into the wells of a cell culture plate having 24 wells, half of which is then additioned with the same culture medium containing the drug at a 10^{-4}M concentration, and harvested in a thermostat at 37°C at a constant moisture. Only the cells coming from said first sub-cultures are used for the experiments with cumene hydroperoxide (CIP). The cells are identified as endothelial cells by morphological examination and by their specific immunological reaction towards factor VIII; said cultures did not show any contaminations from myocytes or fibroblasts.

Before starting the test, the cellular culture medium is removed and the cellular layers are carefully washed with a physiologic solution at a temperature of 37°C. The wells of the culture plate are then incubated for one hour with CIP at a 5 mM concentration in the culture medium. The evaluation of cellular damage (apoptosis) is carried out by determining the per cent variation of the DNA fragmentation with respect to the control group (treated with CIP alone), evaluating the fluorescence variation at the wave length of 405-450 nm. 5 replicates for each sample are carried out.

The drug meets the test, i.e. it can be used for preparing the compounds of general formula (I), when a statistically significant inhibition of apoptosis (cellular damage) induced

by CIP with respect to the group treated with CIP alone is not obtained at $p < 0.01$.

Test 3 (L-NAME): evaluation of the endothelial dysfunction induced by administration of L-NAME (N^W-nitro-L-arginine-methyl ester) J. Clin. Investigation 90, 278-281,1992.

The endothelial dysfunction is evaluated by determining the damage to the gastrointestinal mucosa, the hepatic damage and blood hypertension induced by administration of L-NAME.

The animals (rats) are divided in groups as herein below shown. The group receiving L-NAME is treated for 4 weeks with said compound dissolved at a concentration of 400 mg/litre in drinking water. The following groups are constituted (No. 10 animals for group):

A) Control groups:

1° group: only carrier (aqueous suspension 1% w/v of carboxy-methylcellulose, dose: 5 ml/Kg when the drug is administered by os, phisiologic solution when administered parenterally),

2° group: carrier + L-NAME,

B) Groups administered with the drug:

3° group: carrier + drug,

4° group: carrier + drug + L-NAME.

The administration routes are those known for the drug, and can be the oral or subcutaneous, intraperiteneal, intravenous or intramuscular route. The drug is administered at that dose which results the highest still tolerated by the animals of the group of rats not pretreated with L-NAME, i.e. the highest administrable dose at which there is no evident toxicity in the animals, i.e a toxicity recognizable for its symptoms. The drug is administered once a day for 4 weeks.

At the end of the four weeks treatment access to water is prevented and after 24 hours the animals are sacrificed.

One hour before the sacrifice blood-pressure is determined, and a blood pressure increase is taken as an evaluation of the damage to vascular endothelium. The damage to the gastric mucosa is evaluated as illustrated in test 1 (see example F1). The hepatic damage is determined by evaluation of the glutamic-pyruvic transaminase (GPT increase) after sacrifice.

The drug meets test 3, i.e. it can be used for preparing the compounds of general formula (I), when in the group of rats treated with L-NAME + drug + carrier it is found an higher hepatic damage (GPT) and/or an higher gastric damage and/or an higher cardiovascular (blood-pressure) damage in comparison to that of the group treated with the carrier alone, or of the group treated with carrier + drug, or of the group treated with carrier + L-NAME; even if the drug pharmaco-therapeutic efficacy, assayed by specific tests, is not significantly reduced.

Under the conditions indicated in the above described in vivo tests 1 and 3 the therapeutic index of the drug is reduced since the usual doses at which the drug can be effective are no longer tolerated.

Test 4A is performed according to the method described by R. Maffei Facino, M Carini G. Aldini, M.T. Calloni, Drugs Exptl. Clin. Res. XXIII (5/8) 157-165 1997. Test 4A is a test in vitro wherein erythrocytes isolated by standard methods from Wister male rats (Charles River), are kept for 4 days at 4°C in suspension in a physiological solution buffered at pH 7.4 with phosphate buffer. At the end of said period an aliquot of the suspension is taken and centrifuged at 1000 rpm for 5 minutes. 0.1 ml of the centrifuged erythrocytes are diluted to 50 ml with sodium phosphate buffer pH 7.4, obtaining a suspension of erythrocytes 0.2% by volume. No. 5 aliquots of 3.5 ml each of the diluted suspension are added of 0.1-0.3 ml of an alcoholic solution of cumene hydroperoxide in order to have a 270 μM concentration and then incubated at 37°C. This compound causes cell lysis, said lysis causing an increase of turbidity of the suspension. Cell lysis progress is followed by turbidimetry at 710 nm. By performing readings of optical density (or transmittance) at intervals of 30 minutes, it is determined the time (Tmax) at which there is the maximum of turbidity in the suspension, that corresponds to the maximum amount of cells lysed in the suspension. Tmax is assumed to be the time corresponding to 100% of erythrocyte lysis. For determining the inhibiting effect of the precursors of B on haemolysis induced by cumene hydroperoxide, 0.1-0.2 ml of ethanol solutions of each of the assayed compounds precursors

of B are added to 3.5 ml aliquots of the suspension of centrifuged erythrocytes (No. 5 samples for each compound) in order to have a 2 mM final concentration, and preincubated for 30 minutes. Cumene hydroperoxide is then added in such a quantity to have the same final previously stated molarity, and the percentage of haemolysis inhibition of the compound at Tmax is determined as the ratio, multiplied by 100, between the absorbance given by the suspension of the sample under assay, containing the erythrocytes, the precursor of B and cumene hydroperoxide respectively, and the absorbance of the suspension containing the erythrocytes and cumene hydroperoxide; the compound pecursor of B meets test 4A if it inhibits the haemolysis induced by cumene hydroperoxide by a percentage > 15%;

Test 5 is a colorimetric test wherein 0.1 ml aliquots of 10^{-4} M methanolic solutions of the tested products are added to test tubes containing a solution formed by 0.2 ml of 2 mM desoxyribose, 0.4 ml of phosphate buffer pH 7.4 100 mM and 0.1 ml of 1 mM $Fe^{II}(NH_4)_2(SO_4)_2$ in 2mM HCl. The test tubes are then maintained at 37°C for one hour. Then in each test tube 0.5 ml of a 2.8% solution in trichloroacetic acid water and 0.5 ml of an aqueous 0.1 M solution of thiobarbituric acid are added, in the order. A reference blank is formed by adding to a test tube containing only the above described aqueous solution of reactants 0.1 ml of methanol. The test tubes are closed and heated in an oil bath at 100°C for 15 minutes. A pink coloration is developed the intensity of which is proportional to the quantity of desoxyribose undergone to radical oxidative degradation. The solutions are cooled at room temperature and their absorbances are read at 532 nm against the blank. The inhibition induced by the precursor of B or B_1 or C = $-T_c$-Y-H in the confront of radical productionby Fe^{II} is determined by means of the following formula:

$$(1 - A_s/A_c)X100$$

wherein A_s and A_c are respectively the absorbance values of the solution containing the tested compound + the iron salt and that of the solution containing only the iron salt, the compound meets test 5 when the inhibition percentage of radical production as above defined from the precursor of B is higher

than or equal to 50%. The compound precursor of B according to the present invention does not meet test 5.

Unexpectedly the invention products of formula (I) have an improved therapeutic index, under oxidative stress conditions, compared with the precursor drugs. The compounds of the invention of formula (I) wherein the compound precursor of B meets test 4A but does not meet test 5 can be used, as above said, as drugs for the therapy of moderate oxidative stress conditions. In this sense according to the present invention, are intended conditions of moderate oxidative stress.

For illustrative purposes the above mentioned tests are referred to the following compounds. See the Tables.

Test 1: precursor drug: indomethacin

- Maximum administrable dose to rats: 7.5 mg/Kg p.o. By administering a higher dose a toxicity is manifested, characterized by enteropathy, tremor, sedation until death (within 24 hours).
- The group of rats treated with NEM + indomethacin at the above mentioned dose shows gastrointestinal damages.

Since indomethacin in the groups treated with NEM causes gastrointestinal damages, it meets test 1. Indomethacin can therefore be used as a drug for preparing the compounds (I) of the present invention.

Test 2: precursor drugs: indomethacin, paracetamol and mesalamine

Indomethacin and paracetamol meet test 2 since the cellular damage (apoptosis) inhibition induced by CIP is not significantly different with respect to that of the controls.

Therefore the above drugs can be used as drugs for preparing the compounds (I) of the present invention.

On the contrary mesalamine does not meet test 2, since it inhibits the apoptosis induced by CIP. Therefore mesalamine according to test 2 could not be used as a precursor to prepare the compounds (I) of the present invention. It has been however found that mesalamine submitted to test 1 causes gastrointestinal damages.

Thus also mesalamine can be used as a precursor for preparing the compounds (I) of the present invention.

Test 3 (L-NAME) precurosr drugs: paracetamol, simvastatin, omeprazole

Paracetamol and simvastatin meet test 3 since they cause gastric and hepatic damages greater than those induced both by L-NAME + carrier and by the drug + carrier.

Therefore they can be used as precursors to prepare the compounds (I) of the present invention.

On the contrary it has been found that omeprazole neither causes gastric nor hepatic damages, nor influences blood-pressure. According to test 3 omeprazole could not be used as a precursor for preparing the compounds (I) of the present invention.

Test 4A (test for the precursor of B)

N-methyldiethanolamine shows an inhibition of 54.4% (Table V) of haemolysis induced by cumene hydroperoxide. Therefore it meets test 4A and can be used as precursor of B if it does not meet test 5.

Diethanolamine does not inhibit haemolysis induced by cumene hydroperoxide, and it does not meet test 4A. Therefore this compound cannot be used as precursor of B.

Test 5 (test for the precursor of B)

The Table III relating to said test illustrates that N-methyldiethanolamine does not meet test 5, since it does not inhibit radical production from Fe^{II}. Therefore it can be used as precursor of B.

The compounds of formula (I) according to the present invention can be transformed into the corresponding salts. For example a method for forming salts is the following. When in the molecule of the formula (I) compounds a nitrogen atom is present sufficiently basic so as to be salified, the corresponding salts of said compounds are obtainable by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran with an equimolecular amount of the corresponding organic or inoganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids.

Examaples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acids.

The derivatives according to the invention can be used in

the therapeutic indications of the precursor drug, allowing to obtain the other advantages exemplified hereinafter for some groups of these drugs:

- Anti-inflammatory drugs NSAIDs: the invention compounds result very well tolerated and effective, even when the organism is debilitated and is under conditions of oxidative stress. Said drugs can be used also in those pathologies wherein inflammation plays a significant pathogenetic role, such as for instance, but not limited to, in cancer, asthma, miocardic infarction.
- Adrenergic blockers, of α- or β-blocker type: the action spectrum of the compounds of formula (I) results wider than that of the starting drugs: to a direct action on the smooth musculature the inhibition of the nervous beta-adrenergic signals governing the contraction of the hematic ducts is associated. The side effects (dyspnoea, bronchoconstriction) affecting the respiratory apparatus are lower.
- Antithrombotic drugs: the antiplatelet activity is potentiated and in the case of the aspirin derivatives the gastric tolerability is improved.
- Bronchodilators and drugs active on the cholinergic system: the side effects affecting the cardio-vascular apparatus (tachycardia, hypertension) result lowered.
- Expectorants and mucolytic drugs: the gastrointestinal tolerability results improved.
- Diphosphonates: the toxicity relating to the gastrointestinal tract is drastically lowered.
- Phosphodiesterase (PDE) inhibitors (bronchodilators): the therapeutic efficacy is improved, the dosage being equal; it is therefore possible, using the compounds of the invention to administer a lower dose of the drug and reduce the side effects.
- Anti leukotrienic drugs: better efficacy.
- ACE inhibitors: better therapeutic efficacy and lower side effects (dyspnoea, cough) affecting the respiratory apparatus.
- Antidiabetic drugs (insulin-sensitizing and hypoglycaemizing), antibiotic, antiviral, antitumoral,

anticolitic drugs, drugs for the dementia therapy: better efficacy and/or tolerability.

The drugs which can be used as precursors in the general formula of the compounds of the invention are all those meeting at least one of the above mentioned tests 1, 2, 3. Examples of precursor drugs which can be used are the following:

For anti-inflammatory/analgesic drugs, the following can for example be mentioned:

anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, 5-amino-acetylsalicylic acid, alclofenac, alminoprofen, amfenac, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac sodium, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, oxaceprol, oxaprozin, oxyphenbutazone, parsalmide, perisoxal, phenyl acetylsalicylate, olsalazine, pyrazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicilamide O-acetic acid, salicylsulphuric acid, salsalate, sulindac, suprofen, suxibuzone, tenoxicam, tiaprofenic acid, tiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zomepirac, tomoxiprol;

sulindac, differently from other antiinflammatory compounds FANS, is not a cox-inhibitor;

analgesic drugs: acetaminophen (paracetamol), acetaminosalol, aminochlorthenoxazin, acetylsalicylic 2-amino-4-picoline acid, acetylsalicylsalicylic acid, anileridine, benoxaprofen benzylmorphine, 5-bromosalicylic acetate acid, bucetin, buprenorphine, butorphanol, capsaicine, cinchophen, ciramadol, clometacin, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimepheptanol, dipyrocetyl, eptazocine, ethoxazene, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodone, hydromorphone,